Drugs of gout

BY Dr /Aliaa Omar El-hady

Drugs of gout (1)
==========
Goals in the treatment of gout.

-The first goal is safe and rapid treatment of acute gouty attacks to alleviate pain and to restore joint function. This is usually done with NSAIDs or corticosteroids but colchicine can also be used.

Once this is accomplished,

- the next goal is to prevent recurrent attacks and the future development of destructive arthropathy, tophi formation, and nephrolithiasis with hypouricemic therapy.

Enas Tawakal

أفضل دوا لعلاج النقرس المزمن اية دكتوره

Samarino Helal

متسربعة كدة علي طول يا ايناس😂😂😂😂😂😍😘😳

Drugs of gout - colchicine (2)
==========

Colchicine:
-Is an alkaloid derivative from the plant Colchicum autumnale, has been used in the treatment of acute gout for nearly two centuries and for joint pain since the sixth century.

-It has long been believed that the clinical response of acute arthritis to colchicine was diagnostic for gout, although other inflammatory arthropathies such as familial Mediterranean fever, pseudogout, and acute sarcoid arthritis also respond.

Indication & dose of colchicine??

Colchicine (Colcrys) can be used in the treatment of acute gouty attacks and as prophylaxis against future attacks, especially when hypouricemic therapy is initiated.

Colchicine is available orally in 0.6-mg tablets.

The average dose for prophylaxis is 0.6 mg once or twice daily if the patient has normal renal function.

This completely prevents attacks or significantly lowers their frequency in 80% to 85% of patients followed long-term, with minimal toxicity.

Prophylactic doses usually do not cause GI side effects and
should be continued until the patient is without symptoms of gout for several months.

For acute attacks, colchicine is most effective if given in the first few hours.

A recent study showed that 1.2 mg followed in 1 hour by 0.6 mg provides similar efficacy with less toxicity compared with higher dose regimens.

The dose for colchicine must be reduced (or not used) in patients with severe renal insufficiency, severe hepatic disease, or on medications that are CYP 3A4 inhibitors

(clarithromycin, erythromycin, ketoconazole,ritonavir, calcium channel blockers, others).

Colchicine should be avoided (if possible) in patients on cyclosporine (P-glycoprotein inhibitor). هاااااااااااام جدا

Tacrolimus is less of a problem.

Colchicine is not urate lowering ttt

Aliaa Omar El-hady

ماشى يا باشا عدلناها

Mai Ahmed Prophylaxisلا ولا لمده قد ايه long life

Samarino Helal

وانا كمان اتمني اعرف....الاسالة دي مبتجيش غير بالبراكتيس وانك تقيمي حسب الحالة ظروفها اية

مش بشوفها كتير قوي بصراحةgoutوحالات ال

Samarino Helal

Drugs of gout (3)

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Correct Dosage for Colchicine Therapy

Table 86-1. Correct Dosage for Colchicine Therapy

	ACUTE ATTACK DOSE	CHRONIC PROPHYLAXIS DOSE
CYP 3A4 inhibitors	0.6 mg × 1, followed by 0.3 mg in 1 hour Do not repeat for 3 days	0.3 mg daily
Cyclosporine	0.6 mg × 1 Do not repeat for 3 days	0.3 mg every other day
On dialysis	0.6 mg × 1 Do not repeat for 2 weeks	0.3 mg twice a week
CrCl <30 mL/min	1.2 mg × 1, followed by 0.6 mg in 1 hour Do not repeat for 2 weeks	0.3 mg daily
CrCl <50 mL/min	1.2 mg × 1, followed by 0.6 mg in 1 hour	0.6 mg daily

CrCl, Creatinine clearance.

Yasino Yasoyo Si dose in FMF?

Drugs of gout (4)
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Mechanism of action and pharmacokinetics of colchicine.
==========
Colchicine has no effect on serum urate concentration or on urate metabolism.

It functions as an antiinflammatory agent by inhibiting neutrophil chemotaxis through irreversible binding to tubulin dimers, preventing their assembly into microtubules.

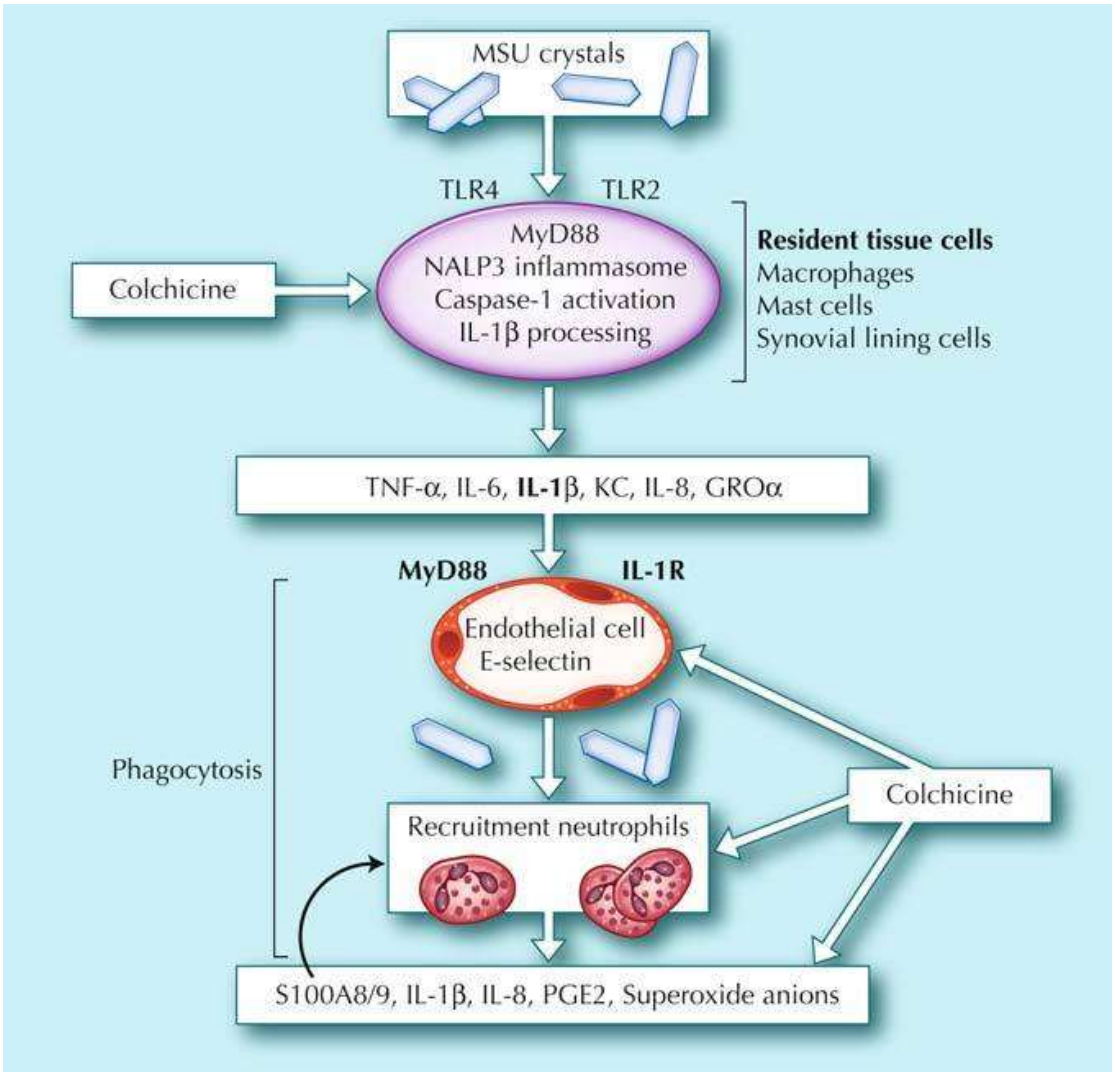
Colchicine also interferes with membrane-dependent functions of neutrophils, such as phagocytosis,and inhibits phospholipase A2, which leads to lower levels of inflammatory prostaglandins and leukotrienes (LTB4).

Colchicine is not bound to plasma proteins and is highly lipid-soluble, readily passing into all tissues.

The half-life is 4 hours following oral administration.

It can be detected in neutrophils up to 10 days after a single dose.

It is hepatically metabolized and excreted principally in the bile, with 20% excreted unchanged in urine.


MSU crystals
TLR4
TLR2
MyD88
NALP3 inflammasome
Caspase-1 activation
IL-1β processing
Colchicine
Resident tissue cells
Macrophages
Mast cells
Synovial lining cells
TNF-α, IL-6, IL-1β, KC, IL-8, GROα
MyD88
IL-1R
Endothelial cell
E-selectin
Phagocytosis
Recruitment neutrophils
Colchicine
S100A8/9, IL-1β, IL-8, PGE2, Superoxide anions

Drugs of gout (5)
==========
Manifestations of colchicine toxicity. هاااااااااااااااام جدا
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Most adverse effects of colchicine are dose and duration related.

There are no antidotes to overdose and hemodialysis is ineffective.

Potential side effects include:

• GI effects (diarrhea, nausea, vomiting, rarely malabsorption syndrome and hemorrhagic gastroenteritis).

• Bone marrow suppression (thrombocytopenia, leukopenia) – risk increased with chronic use and renal insufficiency.

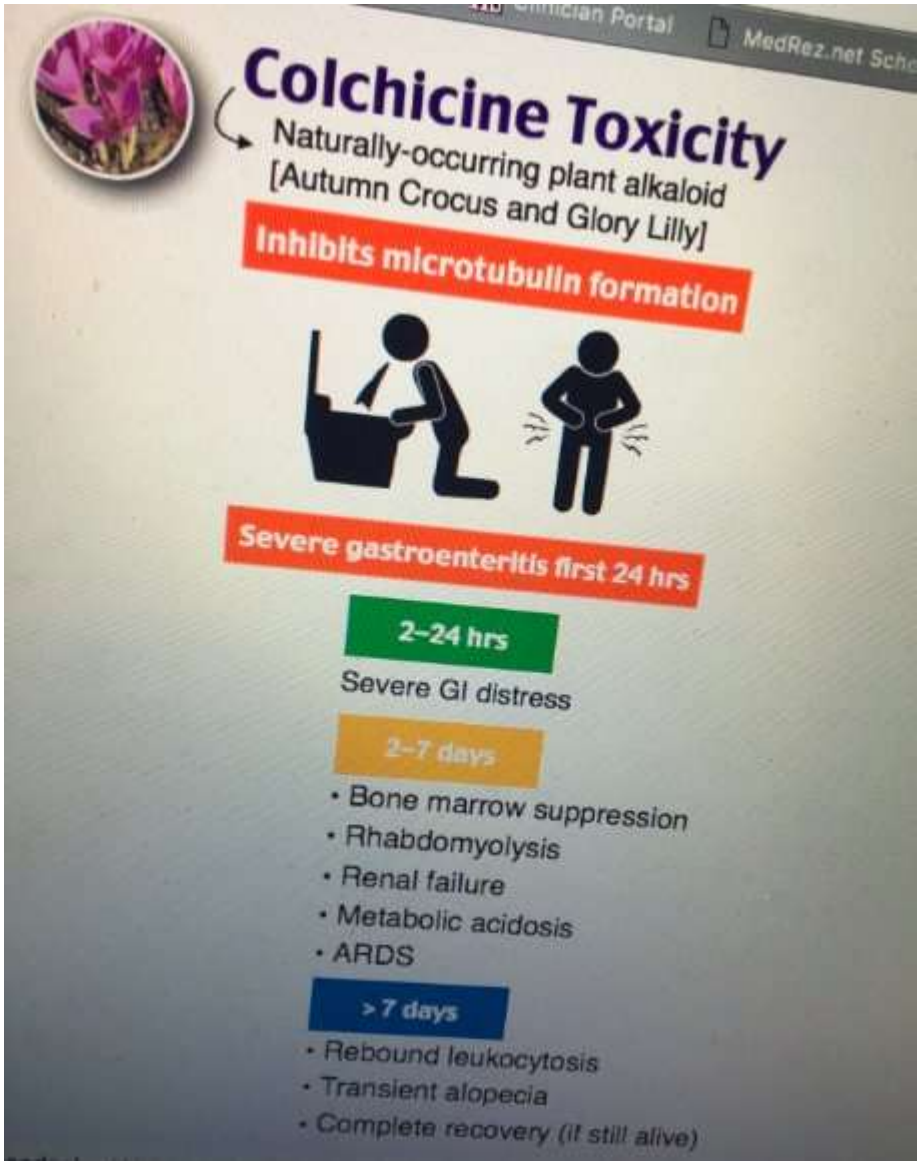
• Neuromyopathy (elevated creatine kinase, proximal weakness, peripheral neuropathy, lysosomal vacuoles on biopsy) – usually seen in patients on chronic colchicine who also have renal insufficiency.

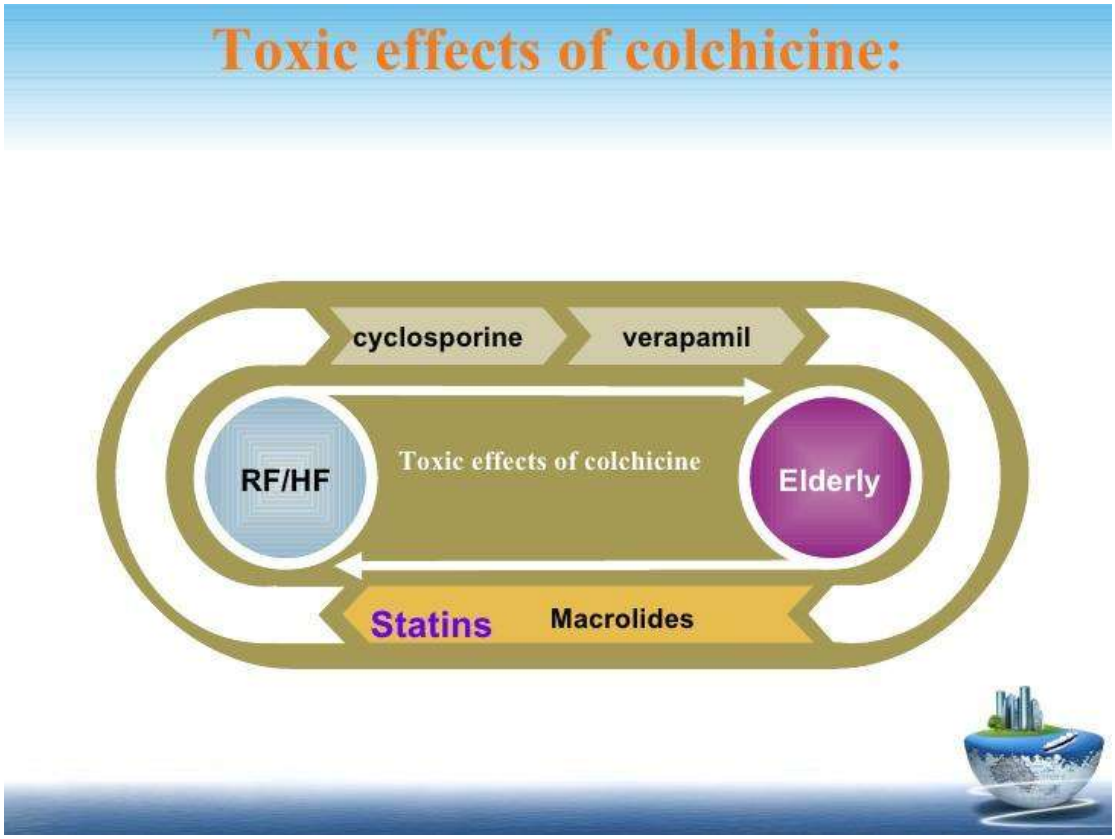
Patients on cyclosporine should not receive colchicine (if possible) because of risk of neuromyopathy.

• Alopecia.

• Oligospermia and amenorrhea – chronic use of colchicine.

• Central nervous system dysfunction.


Clinician Portal
MedRez.net Sch
Colchicine Toxicity
Naturally-occurring plant alkaloid
[Autumn Crocus and Glory Lilly]
Inhibits microtubulin formation
Severe gastroenteritis first 24 hrs
2–24 hrs
Severe GI distress
2–7 days
• Bone marrow suppression
• Rhabdomyolysis
• Renal failure
• Metabolic acidosis
• ARDS
> 7 days
• Rebound leukocytosis
• Transient alopecia
• Complete recovery (if still alive)



الدكتورعمر علي باجخيف Long-term colchicine use can cause neuromuscular complications in patients with decreased renal function, especially older patients.It is caution to avoid more than 0.6 mg of colchicine daily in a patient with a serum creatinine above 1.5 mg/dL. This toxicity manifests with proximal muscle weakness, painful paresthesias, elevated creatine kinase levels, and abnormalities on electromyograms. This axonal neuromyopathy resolves completely over several weeks after discontinuing the colchicine

Drugs of gout (6)
==========
What antihyperuricemic agents are available?
==========
Antihyperuricemic agents include:

1**uricosurics (probenecid), which reduce the serum urate concentration by enhancing renal excretion of uric acid,

2**xanthine oxidase inhibitors (allopurinol and febuxostat), which
inhibit uric acid synthesis by inhibiting xanthine oxidase,

3** the final enzyme involved in the production of uric acid, and uricase (pegloticase), which converts uric acid into allantoin.

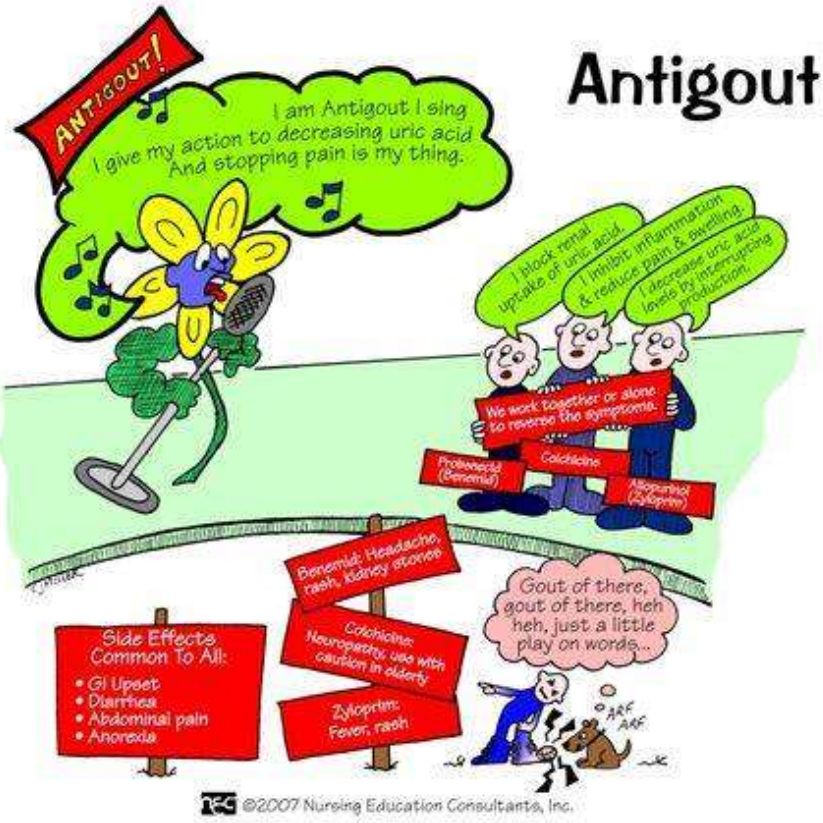
These agents should be initiated only after an acute attack of gout has resolved entirely.

The risk of acute gouty attacks following the initiation of antihyperuricemic therapy can be minimized by gradual dose increases and by prophylaxis with colchicine, NSAIDs, or low-dose prednisone.

The decision to use uric acid-lowering therapy is a lifelong commitment, so it is essential that these agents are initiated only
when they are truly indicated. يعنى ما نستعملهاش عمال على بطال

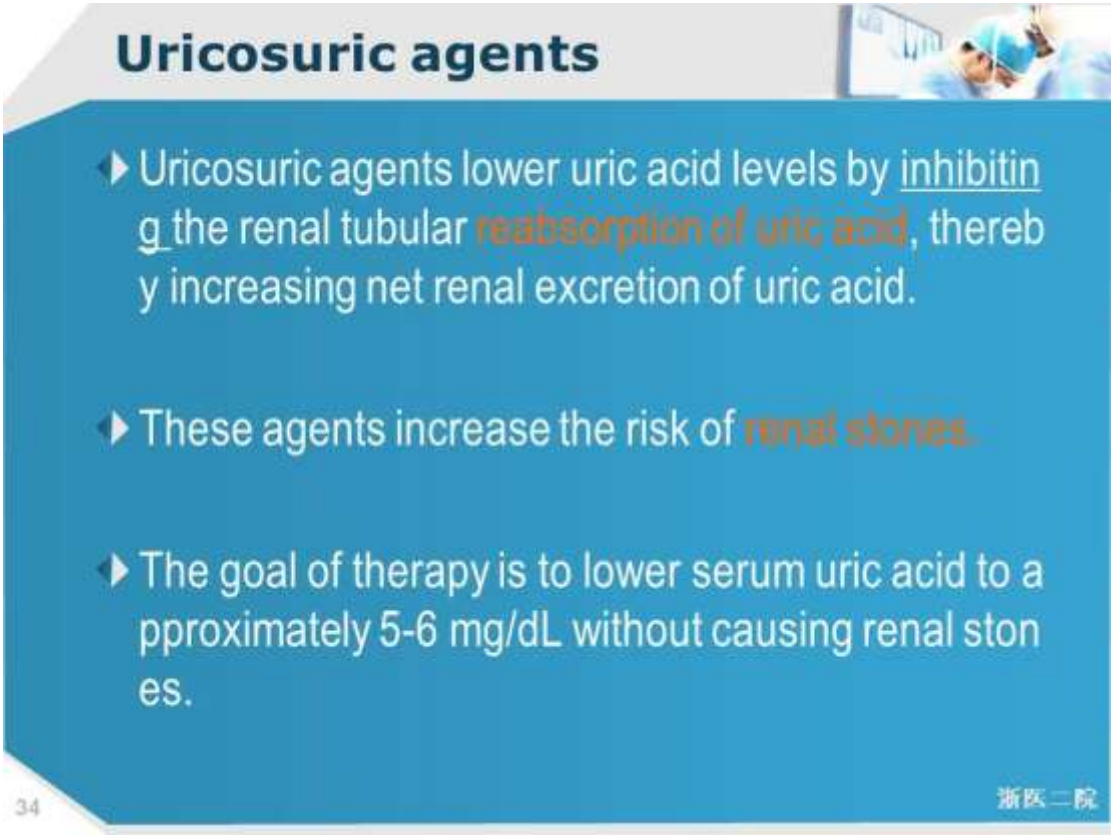
Uricosurics can be safely used concomitantly with allopurinol in some patients with severe tophaceous gout.

Antigout



Drugs of gout (7)
==========
Which patients with recurrent gouty arthritis are the best candidates for uricosuric therapy?

• Hyperuricemia secondary to underexcretion of uric acid (<800 mg of uric acid in a 24-hour urine collection,while on a regular diet).
• Age <60 years.
• Creatinine clearance >50 mL/min.
• No history of nephrolithiasis.
• Uric acid <9 mg/dL (uricosurics reduce urate levels an average of 33%).



Drugs of gout (8)
==========
Renal elimination of uric acid:

Uric acid is excreted primarily (66%) through the kidney.
Up to one third is excreted through the GI tract.
In cases of renal failure, GI excretion is increased.

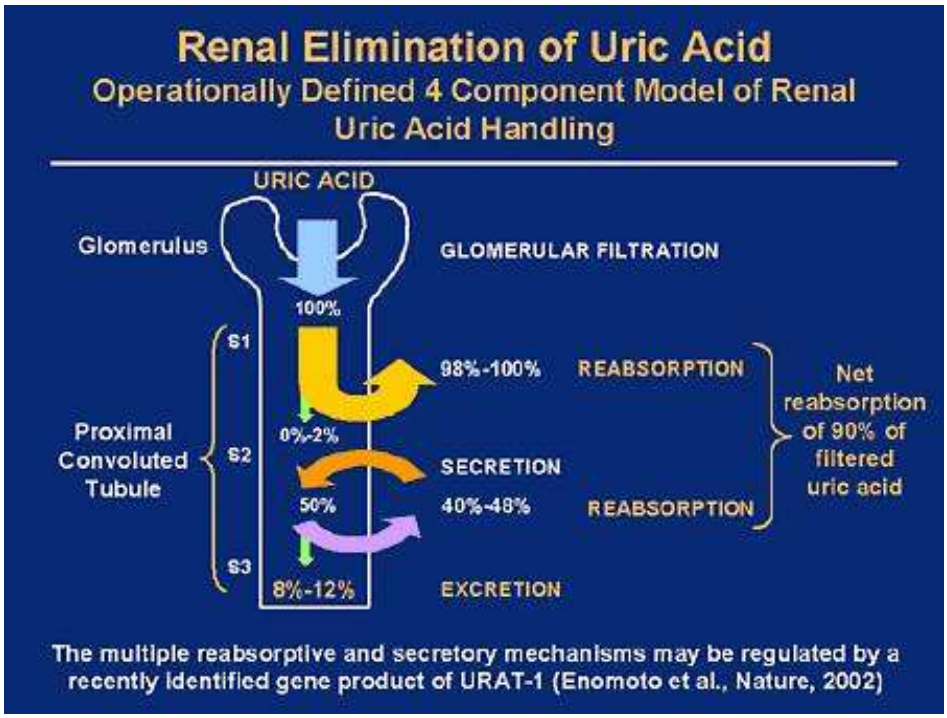
There are four components of renal excretion:

1• Glomerular filtration: near complete excretion of urate.

2• Proximal tubule reabsorption of urate in exchange for organic acids and monocarboxylates (lactate/pyruvate/acetoacetate/ hydroxybutyrate): mediated by URAT1 and GLUT9 transporters.

3• Tubular secretion of urate more distal to above mediated by ABCG2 and MRP4 transporters.

4• Tubular reabsorption of urate a second time in exchange for dicarboxylates (oxalic acid/malonic acid/succinic acid): mediated by OAT4 and OAT10 transporters.



Drugs of gout (9)
==========
Uricosuric agents and their mechanism of action:

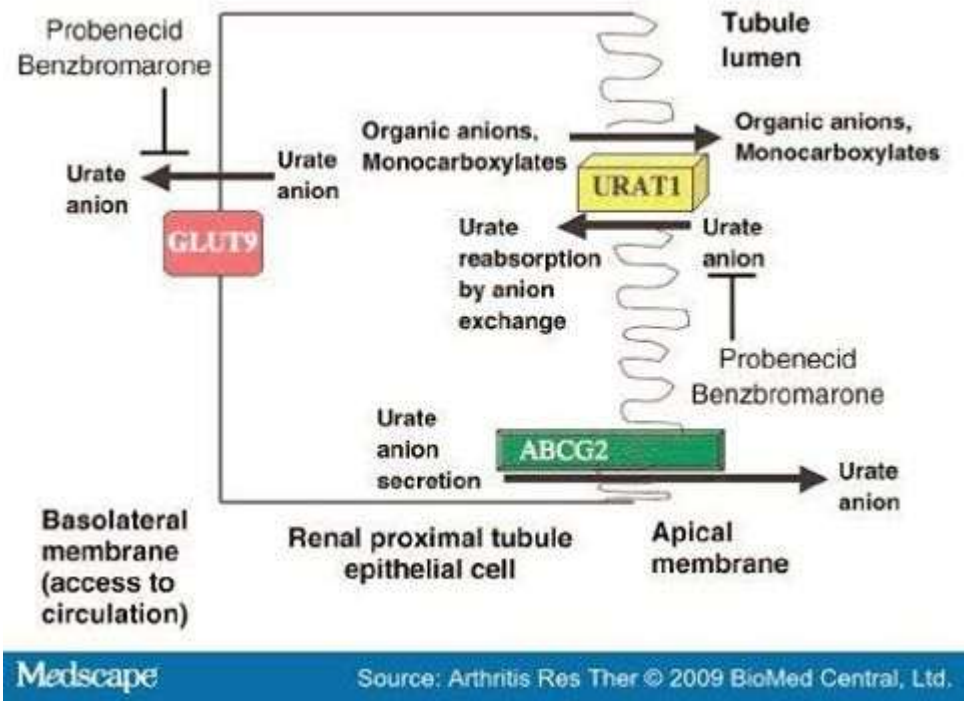
Uricosuric agents (probenecid, Sulfinpyrazone and benzbromarone) are weak organic acids, such as uric acid,
and they inhibit URAT1 and GLUT9 resulting in less tubular reabsorption of urate, which leads to increased urinary excretion of uric acid.

Probenecid (1000 mg twice daily) is successful in lowering serum uric acid to <6.0 mg/dL in 70% of patients.

Uricosurics work better when there is good urine alkalinization (pH >6.0) and flow (>1500 mL/day) to minimize the risk of uric acid nephropathy and nephrolithiasis.

There are several other drugs capable of lowering uric acid levels to a mild degree. These include: losartan,fenofibrate, atorvastatin, rosuvastatin, leflunomide, high-dose (>4 g/day) salicylates. These medications can be safely used in conjunction with other urate-lowering therapies.

PEARL: hypertension is common in patients with gout. Consider using a urate-lowering medication such as losartan to treat hypertension instead of hydrochlorothiazide, which raises uric acid levels.



Tamer Elfarahaty In addation to losartan ; CCB also can be used to decrease risk of gout in HTN. In contrast to Beta blocker ; ACEI (capotril) ; thiazide or loop diuretic which increase risk of gout and it is better to be avoided after internist consultation . Ka sparing diuretics (sprinolactone) are not mentioned as have hyperurcemic effect . By the way ;CCB is one of ist choice for HTN above 55 years .

Samarino Helal

Drugs of gout - Probenecid(10)
==========

• Probenecid should never be started during the acute gout attack. It can be started after the attack has completely resolved.

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If a patient is already on probenecid and experiences a gout attack the patient should not stop the probenecid.

The half-life of probenecid is 6 to 12 hours so it is dosed twice a day.

It is hepatically metabolized.

• Probenecid is available in 500-mg tablets.

It is also formulated as a combination tablet with colchicine
(0.5 mg) (colbenemid).

It is dosed initially at 500 mg twice daily but can be gradually increased up to 3 g daily (average dose 1 g/day) in two to three divided doses.

• Probenecid has multiple possible drug interactions.

هاااااااااام جدا

Therefore, a thorough medication history needs to be taken and investigated before putting a patient on probenecid.

Some examples of interactions:

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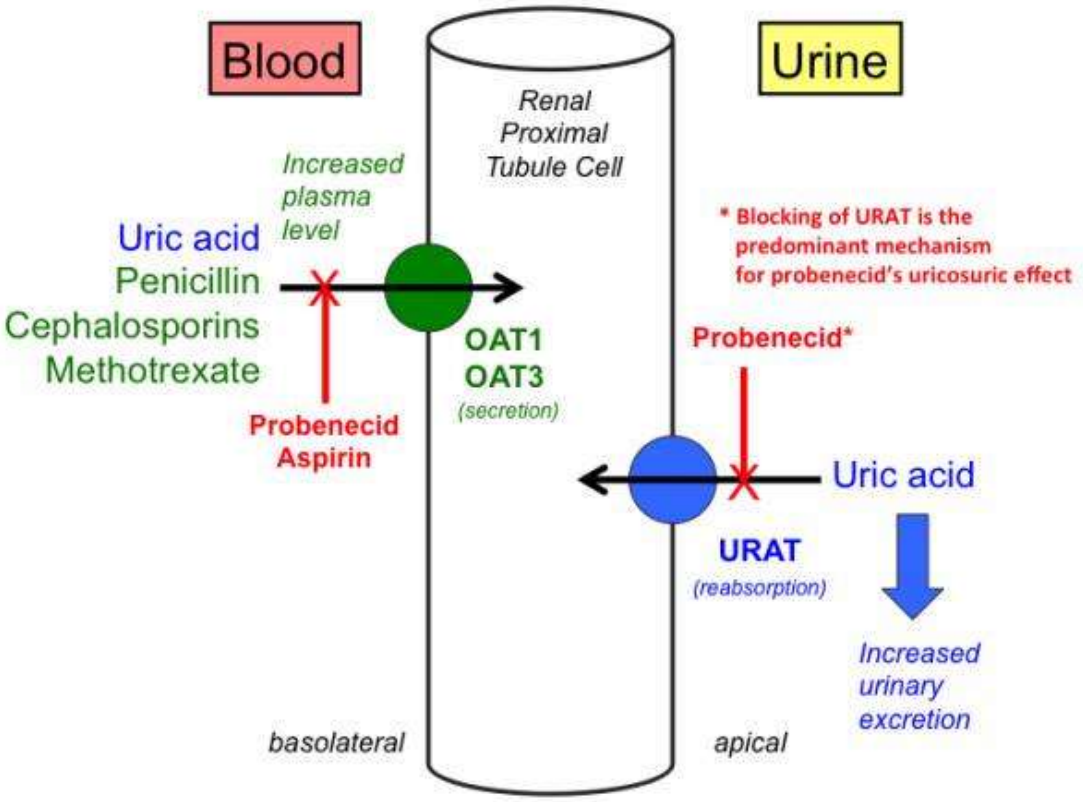
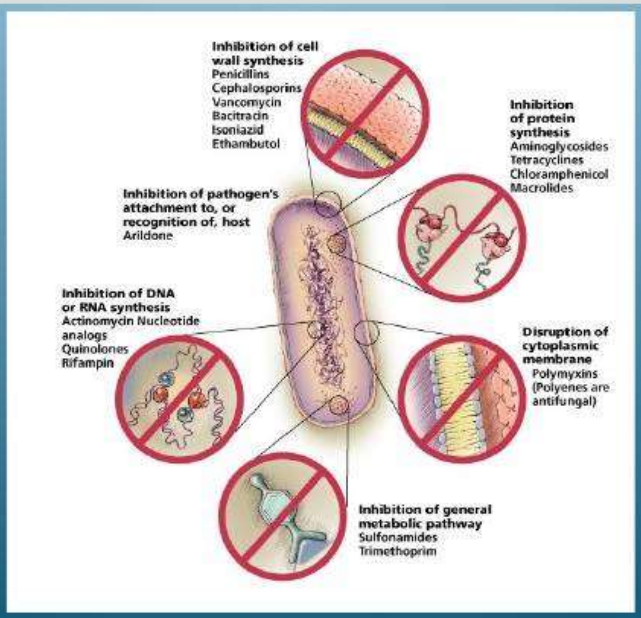
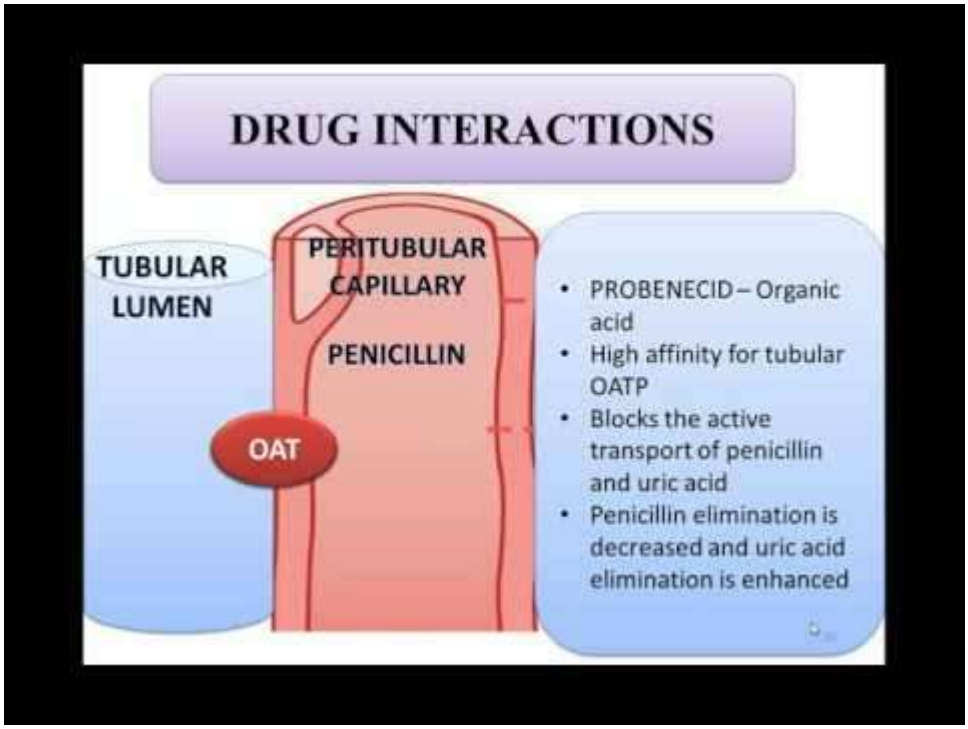
probenecid prolongs the half-life of multiple medications such as penicillin and other antibiotics, dapsone, methotrexate,
indomethacin, and others by decreasing their renal excretion.
It prolongs the metabolism of heparin.



Drug Mechanisms of Action





Marwa Shabana

دكتورة علياء احنا متشكرين جدا على مدي العطاء اللى حضرتك بتقديمه بس يا ريت تكتبي احسن الاسماء التجاريه لأن ذى ما حضرتك عارفة أن فى ادوية كتيره فى الماركت ومش بنفس الجودة وفى اللى نعرفه والله لا

Drugs of gout - Probenecid(11)
==========

Side effects of probenecid therapy:

Probenecid is generally well tolerated by >90% of patients and serious side effects only occur rarely

Preventable :

Acute gouty attacks
Urate nephropathy
Urate nephrolithiasis

Relatively common

Nausea, loss of appetite (10%)
Dermatitis (5%)
Headache, flushing

Rare

Cytopenias
Anaphylaxis
Nephrotic syndrome

Competition:
Probenecid (Benuryl) – Uricosuric

- Dosage: 500 mg BID to 500 mg QID
- Side Effects:

  Headache, anorexia, nausea, vomiting, diarrhea, abdominal discomfort, skin rash, flushing, drug fever, anaphylaxis, increased urination, sore gums, dizziness, hemolytic anemia, and aplastic anemia

- Significant drug-drug interactions:

  methotrexate, indomethacin, ketorolac, zidovudine, dyphylline, nitrofurantoin, doripenem, zalcitabine, amoxicillin, cefditoren pivoxil, cefpodoxime proxetil, cefprozil, choline salicylate, enprofylline, ertapenem, gatifloxacin, ketorolac, lorazepam, norfloxacin, phenprocoumon, piretanide, tenofovir, zidovudine and zomepirac

- Probenecid inhibits multiple transporters of the MRP, OATP and organic anion transporter families (potent inhibition of OAT1 and OAT3 associated with the large number of drug-drug interactions)
- Interactions at URAT1 not thought to contribute to interactions above

Drugs of gout - Sulfinpyrazone and benzbromarone(12)

==========

Benzbromarone

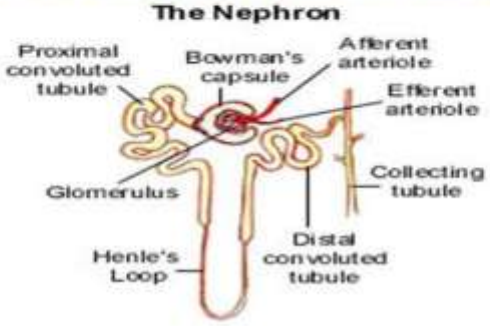
- Benzbromarone (Benzarone) retains its uricosuric effect at doses of 25–150 mg/day in patients who have a creatinine clearance >25 mL/min.
- Good uricosuric effective and safe
- It is effective in mild to moderate disease
- May cause hepatotoxicity
- Limited availability

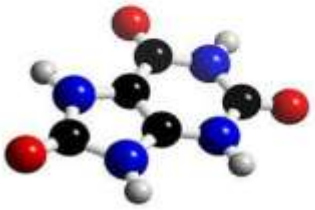
Sulfinpyrazone

- It is a Pyrazolone derivaties related to Phenylbutazone.
- Inhibits tubular reabsorption of uric acid at therapeutic doses.
- Its action is additive with probenecid.
- Use -chronic gout
- Dose :100-200mg BD gradually increase according to the response.

Mechanism of action

- **Uricosuric drugs** (probenecid, sulfinpyrazone, large dose of aspirin)
- block the active transport sites of the proximal tubules(middle segment , decrease the reabsorption of uric acid & increase the amount excreted





Management of Chronic gout (5)Sulfinpyrazone

- A **uricosuric drug** – increases the excretion of uric acid
- Used instead of allopurinol, or in conjunction.
- Dose 100-200mg daily, increasing over2-3 weeks to 600mg(rarely 800mg) daily, until serum uric acid levels normal.

Cautions:

- Hepatic impairment
- Renal impairment
- Pregnancy

Contraindications:

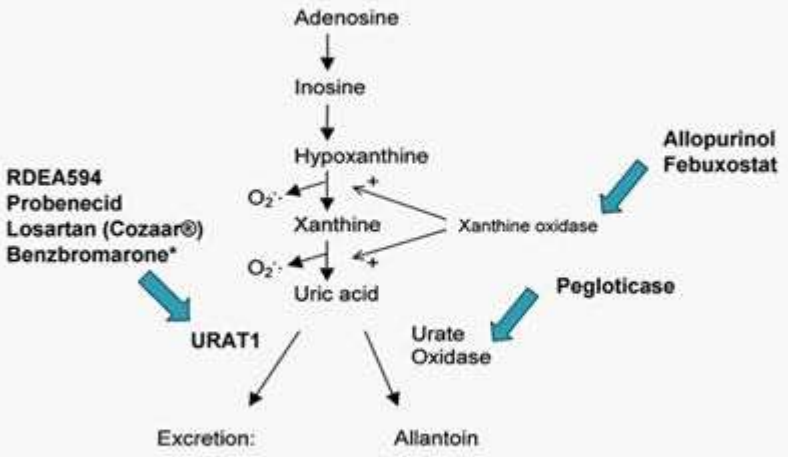
- in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAIDs)
- coagulation defects
- Hx of MI/Stroke or PAD
- moderate or severe heart failure
- active pepticulceration

Drugs of gout - Xanthine Oxidase inhibitors (12)
==========
Xanthine oxidase inhibitors available to inhibit uric acid synthesis are:
• Allopurinol .
• Febuxostat .
The indications for using a xanthine oxidase inhibitor:

In patients with recurrent gout include:
1. Urate overproduction (uric acid >800 mg in 24-hour urine collection on a regular diet).
2. Nephrolithiasis.
3. Renal insufficiency (creatinine clearance <50 mL/min).
4. Tophi (may take several months to resolve).
5. Failure or intolerance of uricosuric agents.

Other indications for a xanthine oxidase inhibitor include:
---
1. Hyperuricemia with nephrolithiasis of any type.
2. Prophylaxis against tumor lysis syndrome.
3. Hypoxanthine phosphoribosyltransferase (HPRT) deficiency (Lesch–Nyhan syndrome).
4. Hyperuricemia attributable to myeloproliferative disorders.
5. Serum urate >12.0 mg/dL or 24-hour urine uric acid >1100 mg.

Uric Acid Production and Elimination



*Benzbromarone is a URAT1 inhibitor approved outside of the US and later withdrawn due to liver toxicity.

Hare, J. M. et al. Circulation 2003;107:1951-1953

Drugs of gout - Xanthine Oxidase inhibitors (13)
==========

The mechanism of action and pharmacokinetic properties of allopurinol compared to febuxostat.

Allopurinol:
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lowers blood and urine urate concentrations by inhibiting the enzyme, xanthine oxidase, thus leading to increases in the precursors, xanthine and hypoxanthine.

Allopurinol is a hypoxanthine analog that is metabolized by xanthine oxidase to the active metabolite, oxipurinol, which can be measured to assess compliance.

Allopurinol is well absorbed from the GI tract and has a half-life of 60 minutes, whereas oxipurinol has a much longer half-life (14 to 28 hours).

The dosage of allopurinol should be lowered in the presence of
renal insufficiency.

The maximum antihyperuricemic effect is seen 7 to 14 days after starting allopurinol.

Febuxostat:
---

is a potent and selective xanthine oxidase inhibitor.
It is 50% absorbed through the GI tract,metabolized by the liver, and has both hepatic and renal excretion.
The maximum antihyperuricemic effect is seen 5 to 7 days after starting febuxostat.

Table 6: Pharmacokinetic parameters of febuxostat and allopurinol[115]

Parameter	Febuxostat	Allopurinol
Absorption (%)	85	67–81
Time to maximum concentration (hours)	1	1
Protein binding (%)	99 (primarily albumin)	Negligible
Volume of distribution (L/kg)	0.7	1.6
Metabolism	Hepatic (glucuronidation 22–44%; oxidation 2–8%)	Hepatic (70% converted to the active metabolite oxypurinol)
Elimination half-life (hours)	8	Allopurinol 1–3; oxypurinol up to 20
Excretion	Renal (<5%, unchanged)	Oxypurinol eliminated unchanged in urine

الدكتورعمر علي باجخيف ¬ The maximum antihyperuricemic effect is seen 7 to 14 days after starting allopurinol.
¬ The maximum antihyperuricemic effect is seen 5 to 7 days after starting febuxostat

Drugs of gout - Xanthine Oxidase inhibitors (14)
==========
How is allopurinol dosed? How is febuxostat dosed?
الجرعات ازای

Allopurinol:
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is available orally in 100- and 300-mg tablets, usually given in once-daily doses.

To limit gout flares and toxicity, current guidelines recommend that allopurinol be started at 100 mg/day and increased by 100 mg
every month.

The average dose used is 300 mg/day but only 40% will achieve the desired urate level goal of <6 g/dL. Therefore, an allopurinol dose of 4 mg/kg to as high as 600 mg/day may be necessary.

One should investigate other correctable factors leading to hyperuricemia if it requires >300 mg/day to achieve adequate uric acid levels, although noncompliance and alcohol abuse are the most common causes.

The dose should be reduced if possible in the presence of renal insufficiency because oxipurinol is renally excreted.

Ideally, the dose should not exceed 200 mg/day when the glomerular filtration rate (GFR) is <60 mL/min, 100 mg/day when GFR is <30 mL/min, and 100 mg every other day when GFR is <15 mL/min.

However, in 50% of patients the allopurinol dose will have to exceed these “renal doses” to achieve the desired uric acid goal.

Febuxostat:
---
is available as a 40-mg and 80-mg tablet, given as a once-daily dose.

It is started at 40 mg/day and subsequently increased to 80 mg/day or 120 mg/day to achieve a goal uric acid of <6 mg/dL.

Experience shows that 70% of patients with tophaceous gout can achieve these levels on 80 to 120 mg/day.

Febuxostat is metabolized by the liver so there is no need to decrease the dose with GFR >30 mL/min. However, it should
not be used in patients with severe hepatic disease.

Neither allopurinol nor febuxostat should be started during an acute gout attack. Either one can be started after the attack is completely resolved.

If a patient experiences a gout attack while receiving one of these drugs they should continue to take them throughout the attack. هاااااااااااااام وما يوقفش الدواء

DOSE ADVANTAGES

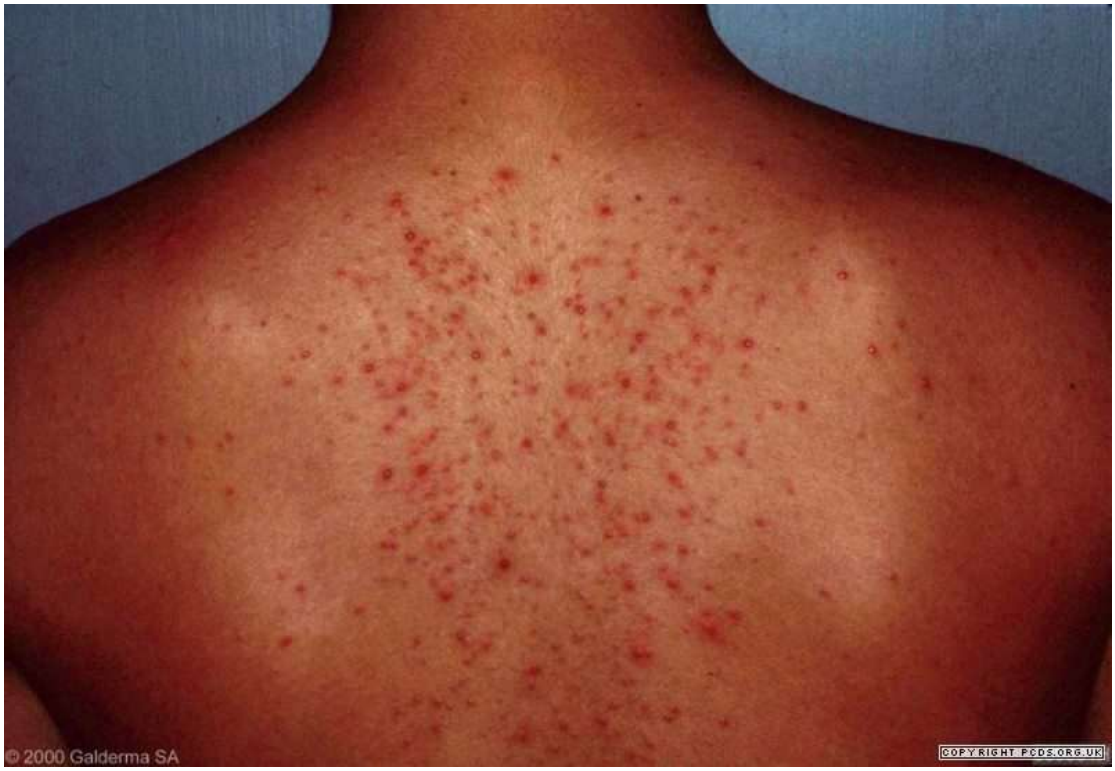
FEBUXOSTAT	ALLOPURINOL
The dosing is 40–mg or 80-mg tablets. Thus, **lesser Dose Dumping** and **lesser dose-related toxicity** (if any).	The dosing is 100-mg or 300-mg tablets. Thus, **greater Dose Dumping** and **greater dose-related toxicity** (if any).
Recommended **starting dose** is 40 mg.	The **minimal effective dosage** is 100 mg daily.
For patients who do not achieve a serum uric acid level of < 6mg/dl after 2 weeks, FEBUXOSTAT 80 mg is recommended.	It is recommended the patient start with 100 mg daily and increase at weekly intervals by 100 mg until a serum uric acid level of < 6 mg/dl is attained.

Drugs of gout - Xanthine Oxidase inhibitors (15)
==========
The major toxicities of allopurinol.

The overall incidence of side effects is around 20%, but only 5% of all patients discontinue therapy as a result of drug toxicity
Common (rarely serious)

Acute gouty arthritis
Maculopapular erythematous rash (3%) – risk is three times
higher if on ampicillin/
amoxicillin
Nausea
Diarrhea
Abnormal liver-associated enzymes (6%)
Headache
Cataracts
Uncommon (potentially serious)

Toxic epidermal necrolysis, exfoliative dermatitis
Oxipurinol xanthine nephrolithiasis
Allopurinol hypersensitivity syndrome (0.1% to 0.4%)
Cataracts
Bone marrow suppression
Sarcoid-like reaction
Hepatitis
Alopecia
Vasculitis
Lymphadenopathy
Peripheral neuropathy
Fever
Renal failure (interstitial nephritis)
Death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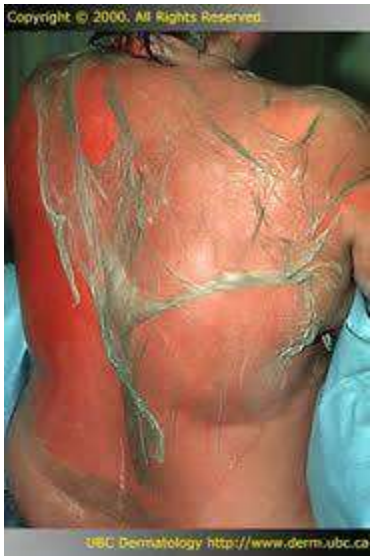
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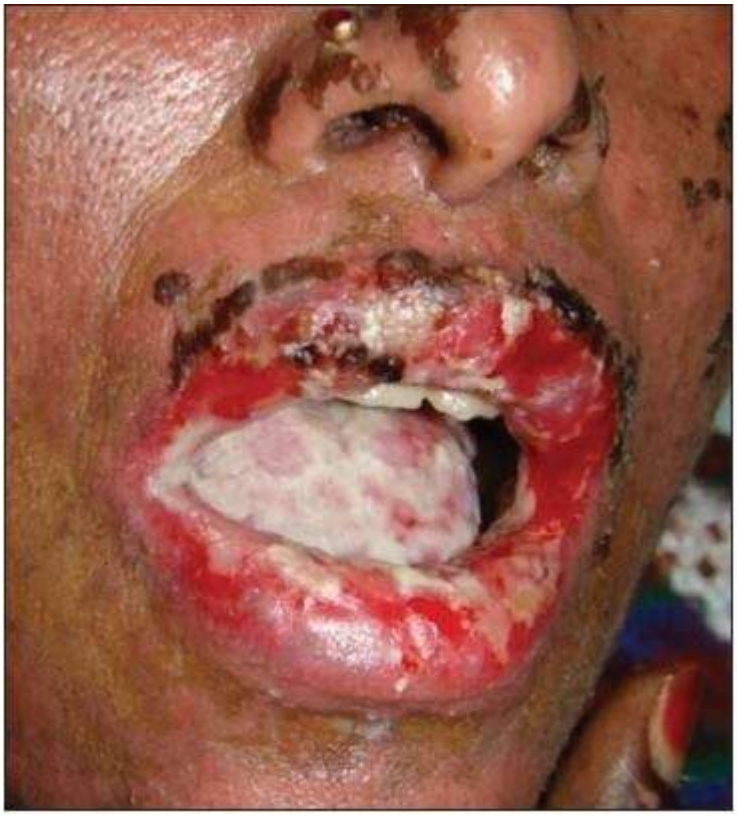


Hanem Salama This side effect disapear when stop i drug or need certain mangment?

Aliaa Omar El-hady

نوقف الدواء ونعالج المضاعفات طبعا

الدكتورعمر علي باجخيف The syndrome of allopurinol hypersensitivity is rare but serious with a mortality rate of 20–30%. Allopurinol hypersensitivity reactions are more common in older patients with impaired renal function taking diuretics. The development of a rash in patients taking allopurinol is an indication to stop the medicine.

Drugs of gout - Xanthine Oxidase inhibitors (16)
==========

The allopurinol hypersensitivity syndrome (AHS):

It occurs in 0.1% to 0.4% of patients.

It is more common (5% to 10% of patients) in patients who have previously developed a maculopapular rash on allopurinol.

Patients who develop this syndrome usually have associated renal insufficiency (75%) and are on diuretic therapy (50%).

Recently, this syndrome has been reported to be associated with HLA-B*5801, which occurs with a frequency of up to 7% in all races.

It is most common in Koreans, Han Chinese, and Thai patients. AHS typically occurs 2 to 4 weeks after initiating therapy, with significant morbidity and a mortality rate as high as 25%.

Clinical manifestations of this syndrome include skin rash, fever, eosinophilia, hepatic necrosis, leukocytosis,and worsening renal function in most patients.

Treatment includes high-dose steroids and hemodialysis (to
remove oxipurinol).

PEARL: Some investigators recommend an allopurinol starting dose of no more than 1.5 mg per unit of estimated GFR to decrease the patient’s risk for getting AHS (e.g., if GFR is 50 mL/min then the starting dose should be no more than 75 mg/day).

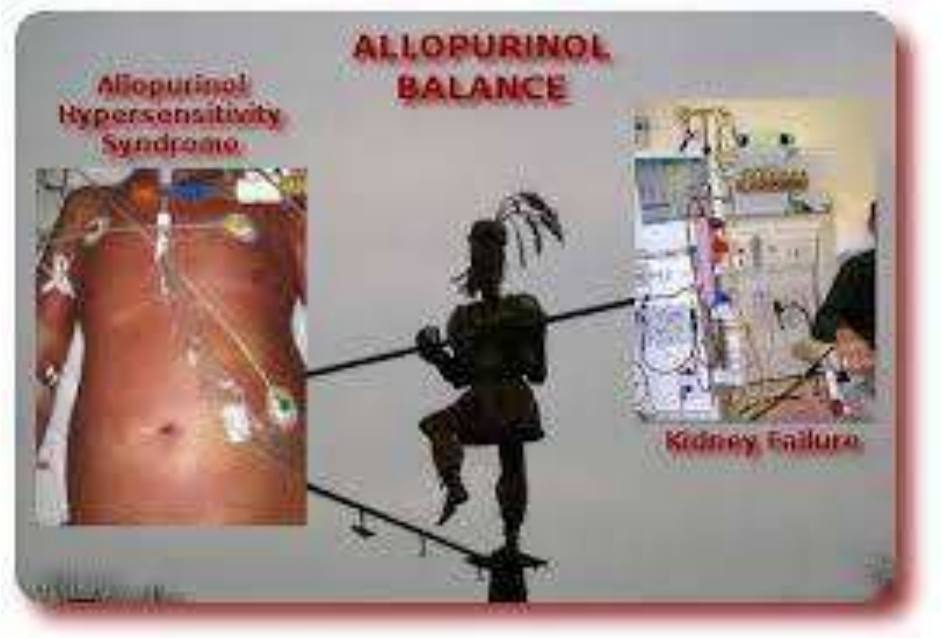
Treatment consists of immediate withdrawal of all suspect medicines, followed by careful monitoring and supportive care. It is very important for patients presenting with a high fever and a rash, where a diagnosis
of drughypersensitivity syndrome is considered, to have blood tests as soon as possible.

Systemic steroids (e.g. prednisone) are generally used in the more severe cases of drug hypersensitivity syndrome involving significant exfoliative dermatitis, pneumonitis and/or hepatitis. However, the benefits of corticosteroids are unknown as controlled clinical trials are lacking. Once effective, they should be withdrawn very slowly as the syndrome can recur as the dose reduces.

Additional treatment may include intravenous immunoglobulins, plasmapheresis, and immunomodulatory drugs such as cyclophosphamide, ciclosporin, mycophenolate and rituximab.

Supportive treatment for the skin rash may include:

Dressings
Topical corticosteroids
Emollients
Oral antihistamines.
Fluid, electrolytes and calorie intake may need attention. A warm environment and expert nursing care are required. Secondary infections may require antibiotics.



Hanem Salama

من رحمة ربنا ان نسبتها قليله

Aliaa Omar El-hady Treatment consists of immediate withdrawal of all suspect medicines, followed by careful monitoring and supportive care. It is very important for patients presenting with a high fever and a rash, where a diagnosis of drug hypersensitivity syndrome is considered, to have blood tests as soon as possible.

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Hanem Salama

جزاكم الله خيرا

Aliaa Omar El-hady

جزانا واياكم

Drugs of gout - Xanthine Oxidase inhibitors (17)
==========
حالة
An organ transplant patient with recurrent gouty arthritis and tophi is referred to you for treatment. His medications include prednisone, cyclosporine, and azathioprine. Laboratories include creatinine 1.8 mg/dL and uric acid 12 mg/dL. What precautions must be taken when prescribing medications for his tophaceous gout?

Acute gout attacks:

• NSAIDs cannot be used, owing to renal insufficiency.
• Adrenocorticotropic hormone cannot be used, owing to lack of adrenal response as the patient is on chronic prednisone.
• Best therapy is oral, intramuscular, or intraarticular steroids.

Chronic suppression:

• Colchicine can be dangerous in patients on cyclosporine. Cyclosporine binds to the multidrug resistance (MDR-1)-related p-glycoprotein (P-gp) that is on the membrane of cells. This protein is an ATP-dependent efflux pump that transports drugs out of liver, renal, and intestinal cells. This transport system is important in hepatic and renal transport of colchicine. Cyclosporine is an inhibitor of MDR-mediated transport causing less colchicine excretion in urine and bile leading to higher colchicine blood levels. Patients most commonly develop a severe neuromyopathy.

Tacrolimus is a weak P-gp inhibitor and thus is less likely to cause colchicine toxicity.

Hypouricemic therapy:

• Uricosuric medications are ineffective in patients with low creatinine clearance.

• Allopurinol and febuxostat inhibit xanthine oxidase, which also breaks down azathioprine. Consequently,azathioprine toxicity is magnified unless its dose is decreased 75%. Even with azathioprine dose reduction,neutropenia commonly occurs.

Therefore, the safer option is to recommend the patient be switched from azathioprine to mycophenolate mofetil, which is not affected by allopurinol or febuxostat.

• Owing to renal insufficiency, allopurinol dose is adjusted to give 100 mg for each 30 mL/min of creatinine clearance. Febuxostat may be a safer choice because it is not renally excreted.

• Pegloticase may be considered to “debulk” his tophi.

Drugs of gout - Xanthine Oxidase inhibitors (18)
==========
Drug interactions with the xanthine oxidase inhibitors:

• Allopurinol:
---
azathioprine and 6-mercaptopurine, which are metabolized by xanthine oxidase, should not be given with allopurinol owing to risk of bone marrow suppression.

Theophylline levels are also increased because it is also metabolized by xanthine oxidase.

Ampicillin/amoxicillin increase the chance of developing an allopurinol rash.

Thiazide diuretics reduce allopurinol excretion, increasing its toxicity. Allopurinol increases cyclophosphamide, warfarin, and cyclosporine levels.

• Febuxostat:
---
because it inhibits xanthine oxidase, coadministration of febuxostat with azathioprine, 6-mercaptopurine,and theophylline should be avoided to limit toxicities.

Allopurinol Drug Interactions

Increase Levels/Effects of Allopurinol	Increase Levels/Effects of Other Medications
Loop Diuretics	Azathioprine
Thiazide Diuretics	6-Mercaptopurine
ACE Inhibitors	Cyclophosphamide
	Amoxicillin
	Ampicillin

الدكتورعمر علي باجخيف Allopurinol reduces the catabolism of azathioprine or 6-mercaptopurine , thereby greatly increasing their effective doses.

liaa Omar El-hady *to* **Drug medications in physical medicine rheumatology & rehabilitation**

22 February ·

2016 updated EULAR evidence-based recommendations for the management of gout
http://ard.bmj.com/.../2016/07/25/annrheumdis-2016-209707.ful...


ARD Online First, published on July 25, 2016 as 10.1136/annrheumdis-2016-209707
Clinical and epidemiological research

EXTENDED REPORT

2016 updated EULAR evidence-based recommendations for the management of gout

P Richette,[1] M Doherty,[2] E Pascual,[3] V Barskova,[4] F Becce,[5] J Castañeda-Sanabria,[6] M Coyfish,[7] S Guillo,[6] T L Jansen,[8] H Janssens,[9] F Lioté,[1] C Mallen,[10] G Nuki,[11] F Perez-Ruiz,[12] J Pimentao,[13] L Punzi,[14] T Pywell,[7] A So,[15] A K Tausche,[16] T Uhlig,[17] J Zavada,[18] W Zhang,[2] F Tubach,[6] T Bardin[1]

Drugs of gout - pegloticase (19)
==========
What is pegloticase?
Unlike other mammals, humans do not have uricase to convert uric acid to the more soluble (5 to 10×) allantoin.

Pegloticase is a recombinant mammalian uricase attached to polyethylene glycol (PEG).

Owing to its cost, it is best used for the treatment of severe (tophi) or refractory (>3 attacks/year) gout patients who cannot lower their
uric acid to <6 mg/dL with xanthine oxidase inhibitors.

Some physicians use it as “induction” therapy to lower the uric acid load in patients with tophaceous gout.

Notably, its pharmacokinetics is not affected by renal function.

Administration & precautions :
==========
• Pegloticase (Krystexxa) is given as a 2-hour intravenous infusion of 8 mg every 2 weeks.

Cost: $2300/infusion.

• All patients must be screened for G6PD deficiency before pegloticase administration.

Do not use in patients with low G6PD enzyme activity.

• All patients should have a serum uric acid before each infusion after the initial dose.

A uric acid level >6 mg/dL indicates there has been a loss of efficacy resulting from development of antipegloticase antibodies.

Development of these antibodies is associated with infusion reactions including anaphylaxis (7%) and thus the infusion should not be given if the uric acid is not low.

• Patients who receive pegloticase should not be continued on other uric acid lowering medications.

This is because use of these medications will keep the uric acid low and the physician will not be able to follow the uric acid level to determine if the patient has developed anti-PEG antibodies.

• All patients should receive premedication (fexofenadine 60 mg night before and before infusion, 1000 mg acetaminophen and Solu-Cortef 200 mg intravenous before infusion) to prevent mild/ moderate infusion reactions, which occur in up to 25% of patients even when the uric acid is <6 mg/dL.

• Pegloticase profoundly lowers the uric acid level within 24 hours and increases the chance of gouty flares (80% of patients).

Patients should receive prophylaxis against gout flares (colchicine, NSAIDs, or prednisone) starting 1 week before starting pegloticase.

Drugs of gout -Lesinurad (20)

==========

Lesinurad (ZURAMPIC) is a URAT1 inhibitor indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated withgout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.

Limitations of Use:

==========

- ZURAMPIC is not recommended for the treatment of asymptomatic hyperuricemia.
- ZURAMPIC should not be used as monotherapy.

DOSAGE AND ADMINISTRATION

==========

- ZURAMPIC is recommended at 200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat. The maximum daily dose of ZURAMPIC is 200 mg.
- Failure to take ZURAMPIC with a xanthine oxidase inhibitor may
increase the risk of renal adverse reactions.
- ZURAMPIC tablets should be taken in the morning with food and water.
- Patients should be instructed to stay well hydrated.
- Assess renal function before initiating ZURAMPIC. Do not initiate
ZURAMPIC if eCLcr is below 45 mL/min.
- Discontinue ZURAMPIC if eCLcr persistently falls below 45 mL/min.

- DOSAGE FORMS AND STRENGTHS

==========

Tablet: 200 mg.

CONTRAINDICATIONS

==========

• Severe renal impairment, end stage renal disease, kidney transplant recipients, or patients on dialysis.

• Tumor lysis syndrome or Lesch-Nyhan syndrome.

WARNINGS AND PRECAUTIONS
==========

• Renal events: Adverse reactions related to renal function have occurred after initiating ZURAMPIC. A higher incidence was observed at the 400 mg dose, with the highest incidence occurring with monotherapy use. Monitor renal function at initiation and during therapy with ZURAMPIC, particularly in patients with eCLcr below 60 mL/min, and evaluate for signs and symptoms of acute uric acid nephropathy.

• Cardiovascular events: Major adverse cardiovascular events were observed with ZURAMPIC; a causal relationship has not been
established.

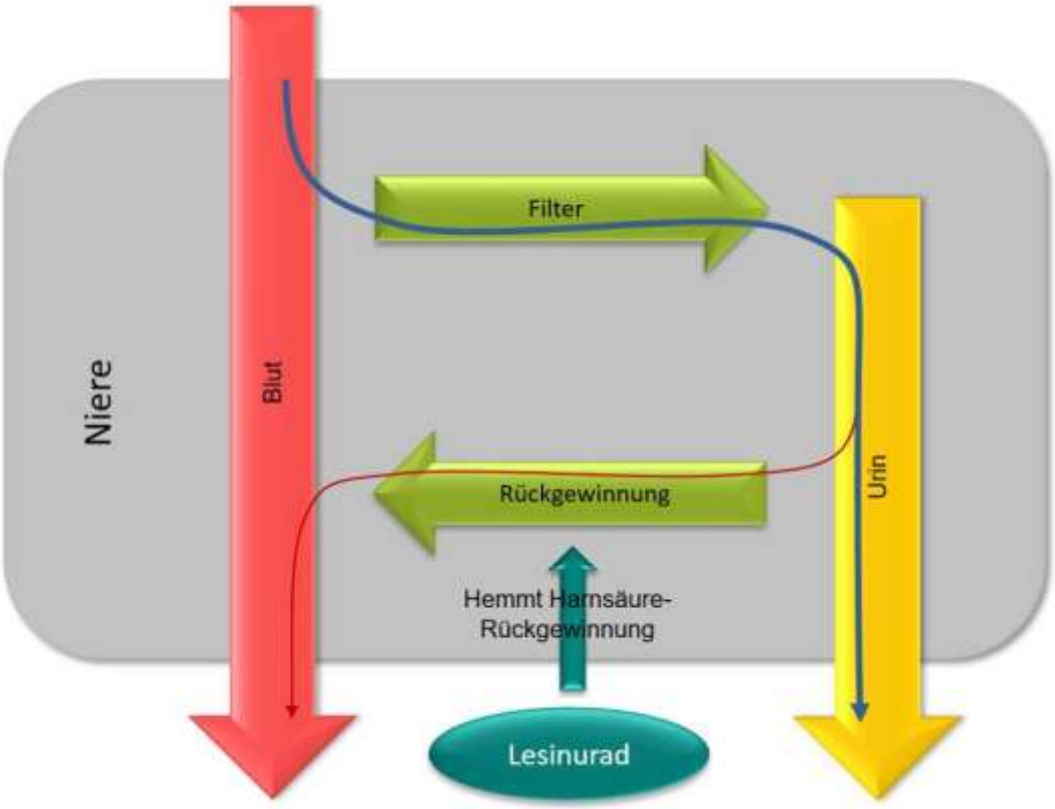
ADVERSE REACTIONS :
==========

Most common adverse reactions in 12-month controlled clinical trials (occurring in greater than or equal to 2% of patients treated with ZURAMPIC in combination with a xanthine oxidase inhibitor and more frequently than on a xanthine oxidase inhibitor alone) were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease.

• Renal impairment: Not recommended for patients with eCLcr below 45 mL/min.

• Hepatic impairment: Not recommended for patients with severe hepatic impairment.


NDC 0310-1475-30
30 Tablets
ZURAMPIC®
lesinurad tablets
200 mg
Dispense the accompanying
Medication Guide to each patient.
Rx only
AstraZeneca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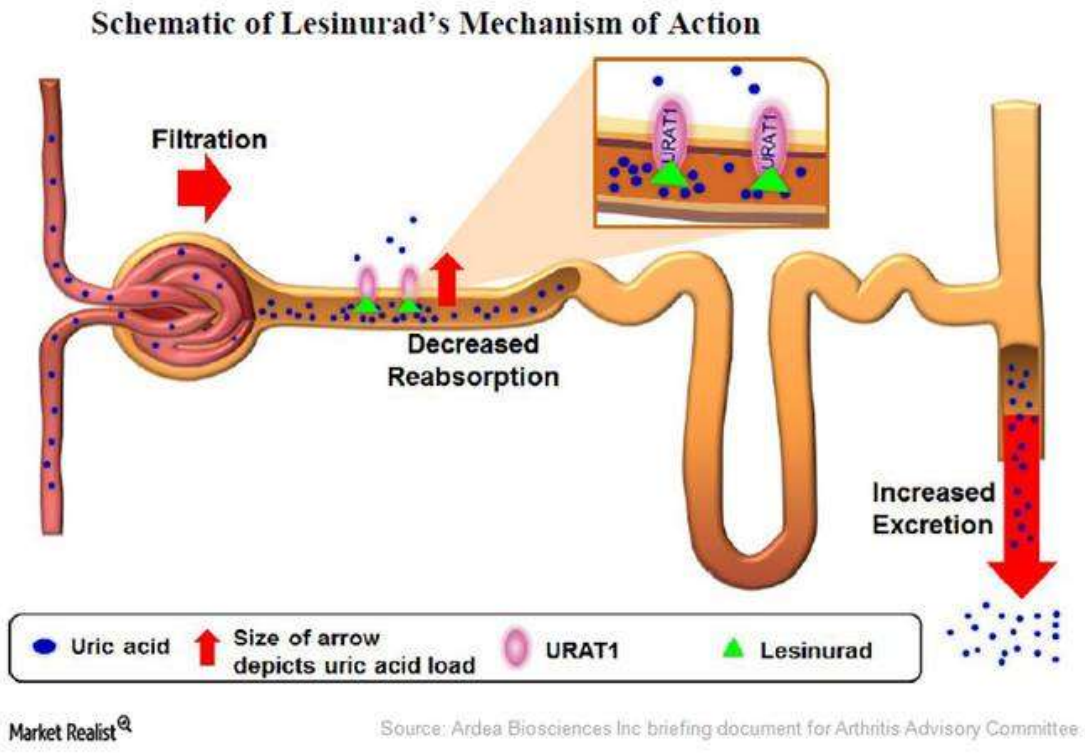

Samar Ibrahim Helal .zurampic.....😊☺ علي وزن زرومبيح

👉👈👉👈👉👈👉👈👉👈👉👈

هل موجود في الماركت عندنا ؟

ولو موجود سعره بكام؟

Aliaa Omar El-hady

Aliaa Omar El-hady

اسألى واعرفيلنا يا استاذة

Samar Ibrahim Helal

.....ربنا يبارك في حضرتك يا أحلي استاذة في الشرق الاوسط وكل الدنيا 😘😉😍
Samar Ibrahim Helal😳😍😉😘😳
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http://www.mapnews.com/1553825/
دواء جديد للحد من معاناة مرضى النقرس
مؤخراً على طرح دواء جديد للحد من FDAوافقت إدارة الغذاء والدواء الأمريكية معاناة مرضى النقرس وذلك عن طريق خفض مستويات حمض اليوريك في...
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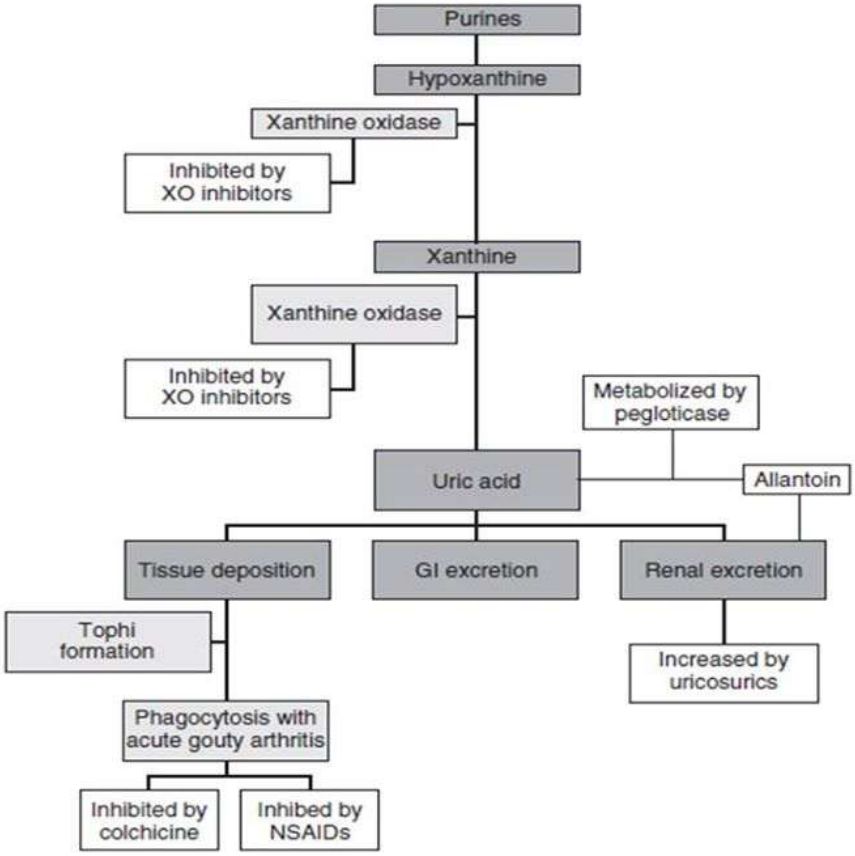
Aliaa Omar El-hady
دى صفحة من الدول العربية مش من مصر
Samar Ibrahim Helal
منا لقيتها عاليوم السابع برضه
ممكن مواقع الجرايد بتنقل من بعضها
http://m.youm7.com/.../%D8%B1%D8%B3%D9%85%D9%8A.../2508363

رسميا..طرح دواء جديد للحد من معاناة مرضى النقرس وتقليل مستويات حمض اليوريك - اليوم...
YOUM7.COM

Aliaa Omar El-hady
المقالتين اللى نزلتيهم هم نفس الكلام بالظبط.. واحد غاشش من التانى ..تفتكرى مين؟؟
Samar Ibrahim Helal
احنا في مصر اساتذة اقتباس 😂😂😂😂😂😂😂
Aliaa Omar El-hady
Samar Ibrahim Helal
بيصوت مننا في كل المحافل😂😂palgarismبرنامج ال
Ayaat Abo Bakr
المرة دي مش احنا اللي مقتبسين المقاتلين نازلين في نفس اليوم بس اليوم السابع نزله الساعة ٢ والموقع التاني نزله الساعة ٣:٤٥ بتوقيت السعودية يعني ٢:٤٥ بتوقيت مصر
براءة المرة دي 😂😂😂

Drugs of gout - (21)
==========
The sites of action for drugs that are used to lower serum urate levels.



Dosing and Safety Information for Currently Available Urate-Lowering Therapies in the Management of Gout

اللى داخل امتحان يحفظها زى اسمه..... من كتاب كيللى ٢٠١٧

TABLE 66-1 Dosing and Safety Information for Currently Available Urate-Lowering Therapies in the Management of Gout

	Dose	Route/ Schedule	Half-life	Primary Site of Metabolism/ Elimination	Adverse Effects	Contraindications (C)/Drug Interactions (DI)
Xanthine Oxidase Inhibitors						
Allopurinol	100-800 mg	PO/daily	1-2 hr (half-life of active metabolite oxypurinol 15-30 hr)	Met: Hepatic xanthine oxidase and aldehyde oxidase (into oxypurinol) Elim: Renal (renal dosing may be required)	Common: Gout flare; skin rash; nausea; diarrhea; LFT abnormalities Rare: Allopurinol hypersensitivity syndrome (AHS) (more common in HLA-B*5801+); cytopenias	C: Concomitant azathioprine, 6-MP, theophylline, prior hypersensitivity DI: Azathioprine, 6-MP, theophylline, ampicillin/amoxicillin, uricosurics, thiazides, cyclosporine, warfarin, ACE inhibitors (possible), Dilantin, cyclophosphamide, vidarabine
Febuxostat	40-120 mg	PO/daily	6-8 hr	Met: Hepatic (glucuronyl conjugation and oxidation via Cyt P450) Elim: Hepatic and renal	Common: Gout flare; skin rash; nausea; arthralgias; LFT abnormalities Rare: Cardiovascular events (unclear association); cytopenias	C: Concomitant azathioprine, 6-MP, theophylline, prior hypersensitivity; severe hepatic impairment DI: Azathioprine, 6-MP, theophylline
Uricosurics					* Adverse effects, contraindications, drug interactions similar for available uricosurics—grouped together below	
Probenecid	500-2000 mg	PO/bid	3-8 hr (500 mg); 6-12 hr (larger doses)	Met: Hepatic (hydroxylation) Elim: Hepatic and renal	Common: Gout flare; nephrolithiasis; rash; flushing; nausea; loss of appetite Rare: Cytopenias, nephrotic syndrome, anaphylaxis, back pain (rare reports of hepatotoxicity with benzbromarone)	C: Prior hypersensitivity; nephrolithiasis; UA overexcretion; concomitantly with other cancer therapies; known blood dyscrasias; active peptic ulcer disease; sulfinpyrazone should be avoided in patients with phenylbutazone/pyrazole allergy DI (more extensive for probenecid/sulfinpyrazone, then benzbromarone): allopurinol, NSAIDs, salicylates, penicillins, cephalosporins, fluoroquinolones, imipenem, rifampin, nitrofurantoin, sulfonamides, heparin, dapsone, acyclovir, ganciclovir, didrouridine, alcohol, diazoxide, mecamylamine, pyrazinamide, antineoplastic agents, clofibrate; dyphylline, diuretics, benzodiazepines, methotrexate, riboflavin, thiopental
Sulfinpyrazone	200-800 mg	PO/bid	3-12 hr	Met: Hepatic (CYP2C9) Elim: Hepatic and renal		
Benzbromarone	50-200 mg	PO/daily	3 hr (half-life of active metabolite 6-hydroxybenzbromarone ~30 hr)	Met: Hepatic (CYP2C9) Elim: Hepatic and renal		
Uricases						
Pegloticase	8 mg*	IV/every 2 wk	Highly variable (days to wk)	Not well defined	Common: Gout flare; allergic reactions; anaphylaxis (~7%); infusion reactions (urticaria, dyspnea, chest discomfort, pruritis, chest discomfort) Rare: CHF exacerbation (unclear association)	C: Allergic reactions to medication or loss of effect (serum UA >6.0 mg/dL indicates development of antipegloticase antibody) DI: Other PEGylated agents (possible)

URATE-LOWERING DRUGS IN DEVELOPMENT

جديد من كيللى ٢٠١٧

Ulodesine (BCX4208) represents a potentially novel mechanism by inhibiting endogenous UA synthesis via the inhibition of purine nucleoside phosphorylase (PNP). Along with adenosine deaminase, PNP plays a role in purine degradation, acting proximally to XO by metabolizing inosine into hypoxanthine. In a 3-week study of 60 patients with gout (all with baseline sUA >8.0 mg/dL), 31% to 36% of patients given ulodesine (40 mg, 80 mg, and 120 mg daily) achieved a final sUA of less than 6.0 mg/dL.[123] Decreases in sUA ranged from 2.7 to 3.4 mg/dL compared with a decline of just 0.4 mg/dL with placebo. Well tolerated in this short-term study, the potential immunosuppressive effects of ulodesine warrant further study, recognizing that inherited PNP deficiency results in severe combined immunodeficiency.

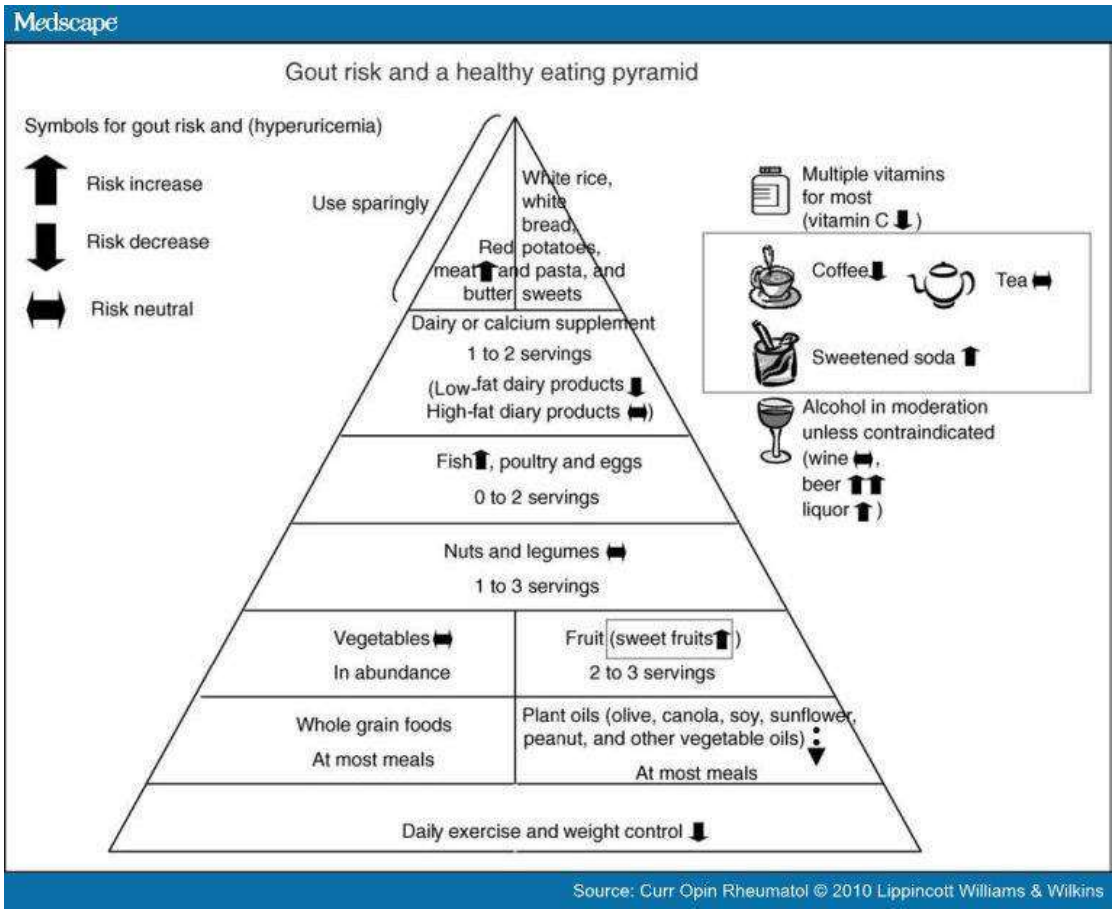
Lesinurad (RDEA594) is a metabolite of RDEA806, a non-nucleoside reverse transcriptase inhibitor, and was approved for use in gout by the U.S. Food and Drug Administration (FDA) in December, 2015. Lesinurad appears to specifically inhibit URAT1 and OAT4, lacking a significant effects on other organic anion transporters (see Figure 66-2).[124] More selective inhibition may limit drug interactions that complicate probenecid use. In contrast to probenecid,[65] the co-administration of lesinurad does not appear to increase the renal elimination of oxypurinol or febuxostat,[125] suggesting that this may be an ideal uricosuric to use in combination with first-line XO inhibitors. The addition of lesinurad to allopurinol (300 mg/day) led to dose-dependent declines in sUA.[126] After the addition of lesinurad (400 or 600 mg/day), the proportion of patients achieving sUA goal of less than 6.0 mg/dL with febuxostat alone (40 or 80 mg/day) increased from between 56% and 67% to 100%.[127]

In addition to displaying urate-lowering properties, tranilast has been studied for possible therapeutic effects in a number of conditions, including allergy, malignancy, and conditions characterized by excessive tissue fibrosis. Similar to currently available uricosurics, the urate-lowering effects of tranilast are mediated through the inhibition of URAT1 and GLUT9 transporters (see Figure 66-2).[128] In a preliminary study, tranilast administration (300 mg/day) was associated with a 14% decline in sUA with 28% of patients achieving a sUA less than 6.0 mg/dL.[129]

A peroxisome-proliferator–activated gamma modulator, arhalofenate (MBX-102) has been highlighted in recent studies as a novel agent demonstrating dual uricosuric and anti-inflammatory effects.[122] In addition to inhibiting renal UA transporters (URAT1, OAT4, OAT10), in vitro studies have shown that the agent effectively blocks monosodium urate–induced production of IL-1. Large-scale human studies of arhalofenate in the treatment of gout have yet to be undertaken.

Levotofisopam is a benzodiazepine derivative approved in countries outside the United States for the treatment of anxiety and autonomic instability and has recently been demonstrated to yield potentially important urate-lowering effects. In an initial proof-of-concept study involving 13 patients with gout, patients were given levotofisopam 50 mg twice daily, with a mean sUA reduction of 49% after 1 week of treatment.[122] The treatment was well tolerated, and all patients achieved a sUA of less than 6.0 mg/dL.

Diet and lifestyle changes for gout



Cyclosporine-Induced Hyperuricemia and Gout

==========

Cyclosporine interferes with the renal excretion of uric acid.

Hyperuricemia and gout occur with increased frequency among transplant recipients treated with cyclosporine and are even more common when diuretics are used concomitantly.

However, serum urate levels do not correlate directly with cyclosporine levels or with the degree of hypertension or renal insufficiency.

The onset of gout may occur soon after transplantation, with a mean of about 17 months.

Gout attacks may be typical and monoarticular,or they may affect unusual sites such as the shoulder, hip,or sacroiliac joints.

Polyarticular attacks and an accelerated course, with early development of tophi, may also be observed.

Nephrolithiasis develops in about 3% of patients who undergo a renal transplant.

All calculi from patients treated with azathioprine are composed of calcium compounds,whereas 60% of the calculi from people treated with cyclosporine contain uric acid.